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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/789,758	02/27/2004	Joseph Cohen	B45187 C1	1891

7590 06/23/2006

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EXAMINER	
MINNIFIELD, NITA M	
ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 06/23/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/789,758	COHEN ET AL.	
	Examiner	Art Unit	
	N. M. Minnifield	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 April 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13 and 16-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13 and 16-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892) 3pgs.
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/11/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

1. Applicants' amendment filed April 11, 2006 is acknowledged and has been entered. Claims 1-12, 14, 15, 23 and 24 have been canceled. Claims 13, 16 and 20 have been amended. Claims 13, 16-22 are now pending in the present application. All rejections have been withdrawn in view of Applicants' amendment to the claims and/or comments, with the exception of those discussed below.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

4. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 13 and 16-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stoute et al (New England J. Medicine, January, 1997, 336:89-91) taken with Davis et al 6406705.

Stoute et al teaches a recombinant vaccine based on fusion of the circumsporozoite protein and HBsAg (RTS,S) plus a potent adjuvant can protect against experimental challenge with *P. falciparum* sporozoites. After additional studies of protective immunity and the vaccination schedule, field trials are indicated for this new vaccine against *P. falciparum* malaria (Conclusion, p. 86; pp. 88-89). Stoute et al teaches a vaccine formulation comprising the RTS,S and two adjuvants, aluminum salt and monophosphoryl lipid A (p. 87). Stoute et al teaches the development of an immunogenic recombinant circumsporozoite vaccine that protects adults who have never been exposed to malaria against

experimental challenge with *P. falciparum* sporozoites (p. 90). "Complete immunity against infection rarely develops from natural exposure, but immunization with radiation-attenuated sporozoites affords full protection. This vaccine strategy is not practical, since it requires repeated exposure to hundreds of infected, irradiated mosquitoes over a period of 6 to 10 months, and sporozoites cannot be cultured in vitro. Nonetheless, these findings revealed a critical role for the circumsporozoite protein in the development of immunity against sporozoite challenge and led to its development as a candidate vaccine. In clinical trials, however, the circum-sporozoite protein is poorly immunogenic, and few subjects have been protected. To address these issues, we created a hybrid in which the circumsporozoite protein fused to hepatitis B surface antigen (HBsAg) was expressed together with unfused HBsAg. The resulting hybrid was significantly more potent than previous circum-sporozoite-protein formulations. We hypothesized that more potent adjuvants could improve the efficacy of the vaccine. We therefore conducted a clinical trial to determine the safety and efficacy of three formulations of circumsporozoite protein vaccines against *P. falciparum.*" (p. 86) Stoute et al teaches the claimed invention except for the use of immunostimulatory CpG oligonucleotides.

However, Davis et al teaches compositions comprising synergistic adjuvants (CpG and non-nucleic acid adjuvant) and antigen (abstract; claims). The antigen can be a parasite antigen (i.e. malarial antigen) (see col. 2; col. 16). The non-nucleic acid adjuvant can be MPL (col. 4; col. 14). Davis et al teaches that the oligonucleotide size can be 8 to 100 nucleotides, preferably 8 to 40 nucleotides (col. 4; col. 11). The prior art specifically teaches the immunostimulatory CpG oligonucleotides as set forth in claim 20. SEQ ID NO: 1, 2 and 6 are identical to

SEQ ID NO: 86/90, 51 and 86/90 respectively (see attached sequence search printout). Davis et al teaches that the composition comprise a "...synergistic combination of adjuvants. The composition includes an effective amount for inducing a synergistic adjuvant response of a combination of adjuvants, wherein the combination of adjuvants includes at least one oligonucleotide containing at least one unmethylated CpG dinucleotide and at least one non-nucleic acid adjuvant. The composition may also include at least one antigen, which may be selected from the group consisting of peptides, polypeptides, cells, cell extracts, polysaccharides, polysaccharide conjugates, lipids, glycolipids and carbohydrates. Antigens may be given in a crude, purified or recombinant form and polypeptide/ peptide antigens, including peptide mimics of polysaccharides, may also be encoded within nucleic acids. Antigens may be derived from an infectious pathogen such as a virus, bacterium, fungus or parasite, or the antigen may be a tumor antigen, or the antigen may be an allergen." (col. 3) "In addition to the use of the combination of adjuvants for prophylactic treatment, the invention also encompasses the use of the combination for the immunotherapeutic treatment of a subject having an infection, an allergy or a cancer. A "subject having an infection" is a subject that has been exposed to an infectious pathogen and has acute or chronic detectable levels of the pathogen in the body. The combination of adjuvants can be used with an antigen to mount an antigen specific immune response that is capable of reducing the level of or eradicating the infectious pathogen. An infectious disease, as used herein, is a disease arising from the presence of a foreign microorganism in the body." (col. 8) It would have been obvious to a person of ordinary skill in the art at the time the invention was made to prepare a composition comprising the RTS,S and adjuvant (CpG or CpG and

aluminum salts) since the prior art teaches that the RTS,S was a better vaccine composition when a combination of adjuvants were present. Further, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to use the CpG adjuvant in a vaccine composition for administration to a human since the art teaches that the CpG is a potent adjuvant and that it induces a Th1-type immune response, including Th1 cytokines such as IL-12 and interferon gamma for protection against various pathogens including parasites. It would have been obvious to a person of ordinary skill in the art at the time the invention was made that there would be a reasonable expectation of success of preventing or ameliorating plasmodium infection in a patient if the prepared composition taught by Stoute et al taken with Davis et al were administered to the patient. Absent any convincing or unexpected evidence to the contrary, the claimed invention is prima facie obvious in view of the combined teachings of the prior art.

6. Claims 13 and 17-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stoute et al (New England J. Medicine, January, 1997, 336:89-91) taken with Krieg et al 6207646.

Stoute et al teaches a recombinant vaccine based on fusion of the circumsporozoite protein and HBsAg (RTS,S) plus a potent adjuvant can protect against experimental challenge with *P. falciparum* sporozoites. After additional studies of protective immunity and the vaccination schedule, field trials are indicated for this new vaccine against *P. falciparum* malaria (Conclusion, p. 86; pp. 88-89). Stoute et al teaches a vaccine formulation comprising the RTS,S and two adjuvants, aluminum salt and monophosphoryl lipid A (p. 87). Stoute et al teaches the development an immunogenic recombinant circumsporozoite vaccine

that protects adults who have never been exposed to malaria against experimental challenge with *P. falciparum* sporozoites (p. 90). "Complete immunity against infection rarely develops from natural exposure, but immunization with radiation-attenuated sporozoites affords full protection. This vaccine strategy is not practical, since it requires repeated exposure to hundreds of infected, irradiated mosquitoes over a period of 6 to 10 months, and sporozoites cannot be cultured in vitro. Nonetheless, these findings revealed a critical role for the circumsporozoite protein in the development of immunity against sporozoite challenge and led to its development as a candidate vaccine. In clinical trials, however, the circum-sporozoite protein is poorly immunogenic, and few subjects have been protected. To address these issues, we created a hybrid in which the circumsporozoite protein fused to hepatitis B surface antigen (HBsAg) was expressed together with unfused HBsAg. The resulting hybrid was significantly more potent than previous circumsporozoite-protein formulations. We hypothesized that more potent adjuvants could improve the efficacy of the vaccine. We therefore conducted a clinical trial to determine the safety and efficacy of three formulations of circumsporozoite protein vaccines against *P. falciparum.*" (p. 86) Stoute et al teaches the claimed invention except for the use of immunostimulatory CpG oligonucleotides.

However, Krieg et al teaches the use compositions comprising a CpG adjuvant and antigen (abstract). The antigen can be a parasite antigen (i.e. malarial antigen) (see col. 11; col. 16). The immunostimulatory oligonucleotides can be used to treat, prevent or ameliorate an immune system deficiency (e.g. parasitic infection) in a subject (col. 6). The non-nucleic acid adjuvant can be conventional adjuvants such as alum (col. 33). Krieg et al teaches that the oligonucleotide size

can be 8 to 40 nucleotides (col. 6; col. 11). The prior art teaches methods of preparing the composition and administering the composition (claims; col. 34). Krieg et al teaches that the compositions can be used to treat, prevent, or ameliorate and immune system deficiency (i.e. parasitic infection) (see col. 6). The prior art specifically teaches the immunostimulatory CpG oligonucleotides as set forth in claim 20. SEQ ID NO: 1, 4 and 6 are identical to SEQ ID NO: 10, 12 and 10 respectively (see attached sequence search printout). It would have been obvious to a person of ordinary skill in the art at the time the invention was made to prepare a composition comprising the RTS,S and adjuvant (CpG or CpG and aluminum salts) since the prior art teaches that the RTS,S was a better vaccine composition when a combination of adjuvants were present. Further, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to use the CpG adjuvant in a vaccine composition for administration to a human since the art teaches that the CpG is a potent adjuvant and that it induces a Th1-type immune response, including Th1 cytokines such as IL-12 and interferon gamma for protection against various pathogens including parasites. It would have been obvious to a person of ordinary skill in the art at the time the invention was made that there would be a reasonable expectation of success of preventing or ameliorating plasmodium infection in a patient if the prepared composition taught by Stoute et al taken with Krieg et al were administered to the patient. Absent any convincing or unexpected evidence to the contrary, the claimed invention is prima facie obvious in view of the combined teachings of the prior art.

7. Claims 13, 17-19 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stoute et al (New England J. Medicine, January, 1997, 336:89-91) taken with Raz et al 6579940.

Stoute et al teaches a recombinant vaccine based on fusion of the circumsporozoite protein and HBsAg (RTS,S) plus a potent adjuvant can protect against experimental challenge with *P. falciparum* sporozoites. After additional studies of protective immunity and the vaccination schedule, field trials are indicated for this new vaccine against *P. falciparum* malaria (Conclusion, p. 86; pp. 88-89). Stoute et al teaches a vaccine formulation comprising the RTS,S and two adjuvants, aluminum salt and monophosphoryl lipid A (p. 87). Stoute et al teaches the development an immunogenic recombinant circumsporozoite vaccine that protects adults who have never been exposed to malaria against experimental challenge with *P. falciparum* sporozoites (p. 90). "Complete immunity against infection rarely develops from natural exposure, but immunization with radiation-attenuated sporozoites affords full protection. This vaccine strategy is not practical, since it requires repeated exposure to hundreds of infected, irradiated mosquitoes over a period of 6 to 10 months, and sporozoites cannot be cultured in vitro. Nonetheless, these findings revealed a critical role for the circumsporozoite protein in the development of immunity against sporozoite challenge and led to its development as a candidate vaccine. In clinical trials, however, the circum-sporozoite protein is poorly immunogenic, and few subjects have been protected. To address these issues, we created a hybrid in which the circumsporozoite protein fused to hepatitis B surface antigen (HBsAg) was expressed together with unfused HBsAg. The resulting hybrid was significantly more potent than previous circum-sporozoite-protein formulations. We hypothesized that more potent adjuvants

could improve the efficacy of the vaccine. We therefore conducted a clinical trial to determine the safety and efficacy of three formulations of circumsporozoite protein vaccines against *P. falciparum.*" (p. 86) Stoute et al teaches the claimed invention except for the use of immunostimulatory CpG oligonucleotides.

However, Raz et al teaches compositions comprising immunostimulatory oligonucleotides (CpG) and antigens (abstract). The antigen can be a parasite antigen (i.e. malarial antigen) (see col. 5; col. 16). The composition can comprise additional adjuvants (col. 6; col. 13-16). Raz et al teaches that the oligonucleotide size can be 6 to more than 20 nucleotides (col. 10). The prior art teaches methods of preparing the composition and administering the composition (col. 12). It would have been obvious to a person of ordinary skill in the art at the time the invention was made to prepare a composition comprising the RTS,S and adjuvant (CpG or CpG and aluminum salts) since the prior art teaches that the RTS,S was a better vaccine composition when a combination of adjuvants were present. Further, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to use the CpG adjuvant in a vaccine composition for administration to a human since the art teaches that the CpG is a potent adjuvant and that it induces a Th1-type immune response, including Th1 cytokines such as IL-12 and interferon gamma for protection against various pathogens including parasites. It would have been obvious to a person of ordinary skill in the art at the time the invention was made that there would be a reasonable expectation of success of preventing or ameliorating plasmodium infection in a patient if the prepared composition taught by Stoute et al taken with Raz et al were administered to the patient. Absent any convincing or unexpected evidence to the contrary, the

claimed invention is prima facie obvious in view of the combined teachings of the prior art.

8. No claims are allowed.

9. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to N. M. Minnifield whose telephone number is

571-272-0860. The examiner can normally be reached on M-F (8:00-5:30) Second Friday Off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette R.F. Smith can be reached on 571-272-0864. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

N. M. Minnifield
Primary Examiner
Art Unit 1645

NMM
June 15, 2006